genetic diseases?, FEBS Lett 359:6-8 (1995)). Several are listed and briefly discussed below.

α1-antitrypsin deficiency. The α1-antitrypsin protein is synthesized in the liver and secreted into the circulation. It serves to prevent damage to the lungs induced by inflammatory processes. Absence of this protein leads to pulmonary scarring and emphysema. In the most common forms of human α1-antitrypsin deficiency, a mutation leads to the synthesis of an α1-antitrypsin molecule which can not fold properly and is consequently not secreted but rather is retained in the liver cell ER (Yu M, Lee K and Kim J, The Z type variation of human alpha 1-antitrypsin causes a protein folding defect, Nature Structural Biology 2:363-367 (1995)).

Paroxysmal Nocturnal Hemoglobinuria. In red blood cells, the inventory of glycosylphosphatidylinositol (GPI) linked proteins includes a pair of polypeptides, Decay Accelerating Factor (DAF) and CD59, which help to protect the erythrocytes from being accidentally injured by complement-mediated cell lysis. One of the proteins which participates in the synthesis of the GPI anchor is a sugar transferase encoded by the PIG-A gene (phospatidylinositol glycan-class A). This gene is located on the X chromosome. In Paroxysmal Nocturnal Hemoglobinuria, a spontaneous mutation occurs in the PIG-A gene in just one of the many precursor cells which give rise to erythrocytes. All of the erythrocytes which arise from this particular precursor, therefore, are deficient in GPI-linked protein synthesis. The transmembrane precursors of the GPI-linked proteins are retained in the ER and degraded. Consequently, these cells lack DAF and CD59 expression and are susceptible to complement attack and lysis. Patients with Paroxysmal Nocturnal Hemoglobinuria are likely to become anemic and can suffer life threatening disorders of clotting and bone marrow function. A treatment which liberated the transmembrane precursors of GPI-linked proteins from the ER and allowed them to travel to the cell surface might prevent or ameliorate the symptoms of this disease.

Familial Hypercholesterolemia. The disease known as Familial Hypercholesterolemia (FHC) is caused by a defect in the gene encoding the low density lipoprotein (LDL) receptor which results in the synthesis of receptors that can not internalize LDL from the cell surface (Goldstein *et al.*, Receptor-Mediated Endocytosis: Concepts Emerging from the LDL Receptor System, Ann. Rev. Cell Biol. 1, 1-39 (1985)). In the absence of functional LDL receptors, cells are unable to import exogenous cholesterol. Even though serum cholesterol levels rise to extraordinarily high levels, cells are unaware of its presence since they lack the machinery that allows them to endocytose

LDL. The excess cholesterol synthesis results in the build up of cholesterol-filled lipid droplets in cells throughout the body. Accumulation of these cholesterol inclusions in the smooth muscle cells that populate arterial walls produces atherosclerotic plaques, which can go on to occupy and occlude the lumens of the blood vessels themselves. A subset of the mutations in the gene encoding the LDL receptor which lead to FHC in humans (the class II mutations) lead to the synthesis of LDL receptors which can not fold properly and which are retained in the ER (Yamamoto *et al.*, Deletion in cysteine-rich region of LDL receptor impedes transport to cell surface in WHHL rabbit, Science 232:1230-1237, 1986). Consequently, they can not participate in the internalization of plasma LDL-bound cholesterol. Pharmacologic treatments which liberate these mis-folded LDL receptors from the ER and allowed them to proceed to the cell surface might allow them to function properly in cholesterol metabolism and prevent the formation of atherosclerotic plaques.

Tay-Sachs Disease. A number of human diseases have been traced to genetic deficiencies in specific lysosomal hydrolases (Griffiths *et al.*, The Mannose-6-Phosphate Receptor and the Biogenesis of Lysosomes, Cell 52:329-341 (1988)). Children who suffer from Tay-Sachs disease, for example, carry a homozygous mutation in the gene encoding the lysosomal enzyme hexosaminidase A. Consequently, their lysosomes are unable to degrade substances containing certain specific sugar linkages. Since they can not be broken down, these substances accumulate in lysosomes. Over time they come to fill the lysosomes, which swell and crowd the cytoplasm. The resulting derangements of cellular function are toxic to a number of cell types and ultimately underlie this disease's uniform fatality within the first few years of life. At least one mutation which has been shown to induce Tay-Sachs disease leads to deletion of the last 22 amino acids of the protein, preventing its proper folding (Lau MMH and Neufeld EF, A frameshift mutation in a patient with Tay-Sachs disease causes premature termination and defective intracellular transport of the alpha-subunit of beta-hexosaminidase, J Biol Chem 264:21376-21380 (1989)). The mutant protein is retained in the ER and does not travel to its site of functional residence in the lysosome. Releasing this protein from the ER might prevent the Tay-Sachs pathology in patients who carry this allele.

Immune surveillance of tumors and virally infected cells. In order for the immune system to detect and destroy tumor cells and virally infected cells, these target cells must present peptide fragments derived from tumor or viral antigens at their cell surfaces in association with MHC class I molecules. These peptide fragments are derived from proteasome-mediated digestion of the foreign antigens followed by TAP-mediated

transport of these fragments into the lumen of the ER, where they can assemble with MHC class I and β2-microglobulin to form the mature MHC complex. Only the mature, peptide-containing MHC complex can depart the ER and be transported to the cell surface. In the absence of peptides in the lumen of the ER, the incompletely assembled MHC I-β2-microglobulin complex is retained in the ER through interactions with calnexin.

Several viruses and tumors avoid immune detection by blocking the surface expression of the mature MHC class I complex. The herpes simplex virus induces host cells to synthesize the ICP47 protein, which directly inhibits the TAP transporter (Hughes E, Hammond C and Cresswell P, Mis-folded major histocompatibility complex class I heavy chains are translocated into the cytoplasm and degraded by the proteasome, PNAS 94:1896-1901 (1997)). In a number of tumors, expression of the genes encoding the two polypeptides which constitute the TAP transporter is lost (Pogador *et al.*, Natural killer cell lines kill autologous β2-microglobulin-deficient melanoma cells: Implications for cancer immunotherapy, PNAS 94:13140-13145 (1997)). Consequently, the immune system is unable to respond adequately to the pathologic condition. To assist the immune system in recognizing and destroying virally infected or transformed cells, it might be desirable to release the peptide-free MHC class I-β2-microglobulin complex from calnexin-mediated ER retention. This complex would then travel to the cell surface, where it could associate with a specific peptide, administered to the patient by infusion and chosen to maximize the immunogenicity of the resulting peptide-MHC-class I-β2-microglobulin complex. Thus, drugs which release mis-assembled proteins from the ER might prove efficacious in the treatment of a variety of viral and neoplastic diseases.

Hereditary Myeloperoxidase Deficiency. Phagocytes, in particular neutrophils, respond to stimulation with a burst of oxygen consumption. The oxygen consumed is converted to hydrogen peroxide by myeloperoxidase (MPO), which is released from the neutrophil granules, and a complex is formed that is capable of oxidizing a large variety of substances, and that has, as a result, important anti-microbial properties (Klebanoff, Myeloperoxidase, Proc. Assoc. Am. Physicians, 111(5):383-389, 1999).

In the endoplasmic reticulum, MPO precursors interact transiently with calrecticulin and calnexin, presumably as molecular chaperones. MPO deficiency is a relatively common disorder, and several missense mutations have been identified where the mutant precursor is retained in the endoplasmic reticulum due to prolonged binding to calnexin. The mis-folded protein is eventually degraded (Nauseef, *Quality Control in the Endoplasmic Reticulum: Lessons from Hereditary Myeloperoxidase Deficiency*, J. Lab.